Bubbly lupus: A case of a Filipino woman with bullous systemic lupus erythematosus successfully treated with prednisone and hydroxychloroquine

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Bullous systemic lupus erythematosus (BSLE) is an autoimmune-mediated, chronic, widespread, non-scarring, sub-epidermal blistering skin disease. It is typically caused by autoantibodies against type VII collagen. BSLE is an uncommon manifestation of SLE and is found in less than 5% of SLE cases.

We report a case of a 21-year-old woman with a two-year history of systemic lupus erythematosus who developed multiple pruritic vesicles on the neck six weeks prior to consultation. The lesions increased in number, size, and distribution, becoming bullae on the face, trunk, upper and lower extremities. Nikolsky and Asboe – Hansen signs were negative. Mucosal involvement and visceral organ impairment were not identified on physical examination. A 4-mm skin punch biopsy of a vesicle showed a subepidermal blister. Direct immunofluorescence of perilesional skin revealed linear deposits of IgG (+1), C3 (+1), IgM (+2) and granular fibrinogen (+2) at the basement membrane zone, consistent with bullous systemic lupus erythematosus. Oral prednisone 40 mg/day and hydroxychloroquine 200mg once a day were prescribed. The lesions became dry and flat after two weeks and no new eruption was noted after three months.

Patients with BSLE manifest with a widespread symmetrical distribution of vesicular skin lesions frequently favoring the upper part of the trunk, flexural and extensor aspects of the upper extremities, neck and face but may occur anywhere on the cutaneous surface. Treatment with corticosteroids and hydroxychloroquine was effective in our case. The prognosis of BSLE is good with variable duration characterized by spontaneous exacerbations and remissions influenced more by the systemic disease rather than by the eruption hence the need to follow closely the systemic disease activity.

Keywords: bullous systemic lupus erythematosus, lupus, prednisone, hydroxychloroquine

INTRODUCTION

Most patients with systemic lupus erythematosus (SLE) develop cutaneous manifestations. However, bullous skin lesions are uncommon and are found in less than 5% of such patients.[1,2] Bullous systemic lupus erythematosus (BSLE) is a sub-epidermal blistering disease that occurs in a group of patients with systemic lupus erythematosus (SLE).[2-4] It is characterized histologically by subepidermal bullae with the predominance of neutrophilic infiltrates and the deposition of immunoglobulins and C3 on the basement membrane zone including circulating antibodies to Type VII collagen [5].

CASE SUMMARY

The patient is a 21-year-old woman who was diagnosed to have systemic lupus erythematosus since two years prior to consult based on the presence of a malar rash, photosensitivity, oral ulcers, arthritis, telogen effluvium, anemia, presence of anti-nuclear antibodies(ANA), and proteinuria. She was initially maintained on prednisone 40mg per day and hydroxychloroquine 200mg/tablet once a day that controlled the manifestations of SLE.

Six weeks prior to consult, the patient noted multiple pruritic vesicles on the neck arising from normal skin. The lesions increased in size and number, with bullae appearing on the face, trunk, and hands, upper and lower extremities. The lesions became crusted and eroded. The patient sought consult at a health center and was initially diagnosed with varicella zoster. She was then referred to a different hospital where she was admitted and treated as a case of bullous impetigo. The patient was given oral ofloxacin, oral paracetamol and mupirocin ointment. The prednisone and hydroxychloroquine were discontinued. The lesions eventually dried up leaving multiple hyperpigmented macules and patches without scarring. No new lesions were noted and the patient was discharged after one and a half weeks.

Two weeks prior to consult, there was a recurrence of vesicular lesions on both upper and lower extremities with no associated systemic symptoms. The patient sought consult with her rheumatologist who resumed the patient's prednisone at 40mg/day and hydroxychloroquine 200mg/tablet once a day. She was referred to our institution for further evaluation.

On physical examination, there were multiple tense vesicles and well – defined irregular erythematous to hypopigmented macules and patches with crusts and

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erosions on the face, neck, trunk, and bilateral upper and lower

extremities (Figure 1). There were no mucosal lesions. Nikolsky and Asboe Hansen signs were negative. No extracutaneous manifestations of SLE were noted on physical examination.

Our initial impression was bullous systemic lupus erythematosus. A 4-mm skin punch biopsy of a vesicle was done and revealed focal atrophy of the epidermis with vacuolar alteration of the basal cell layer and a sub-epidermal blister containing fibrin, lymphocytes and many neutrophils. There was thickening of the basement membrane zone and the dermis revealed numerous pigment-laden macrophages and a mild superficial perivascular and periadnexal inflammatory infiltrate consisting of lymphocytes, neutrophils and few eosinophils (Figure 2). These findings were consistent with BSLE.

Direct immunofluoresence of perilesional skin showed linear deposits of IgG (+1), C3 (+1), IgM (+2) and granular fibrinogen (+2) on the basement membrane zone, also consistent with BSLE (Figure 3).

Prednisone 40 mg/day and hydroxychloroquine 200mg/tablet once a day were continued. There was flattening and drying of the lesions after two weeks. Prednisone was tapered down by her rheumatologist to 5mg/tab once a day and hydroxychloroquine was tapered down to 50mg/day. Follow-up after three months revealed no new eruptions of vesicles and bullae while maintained on the said regimen (Figure 4). No scarring from the previous lesions were noted.

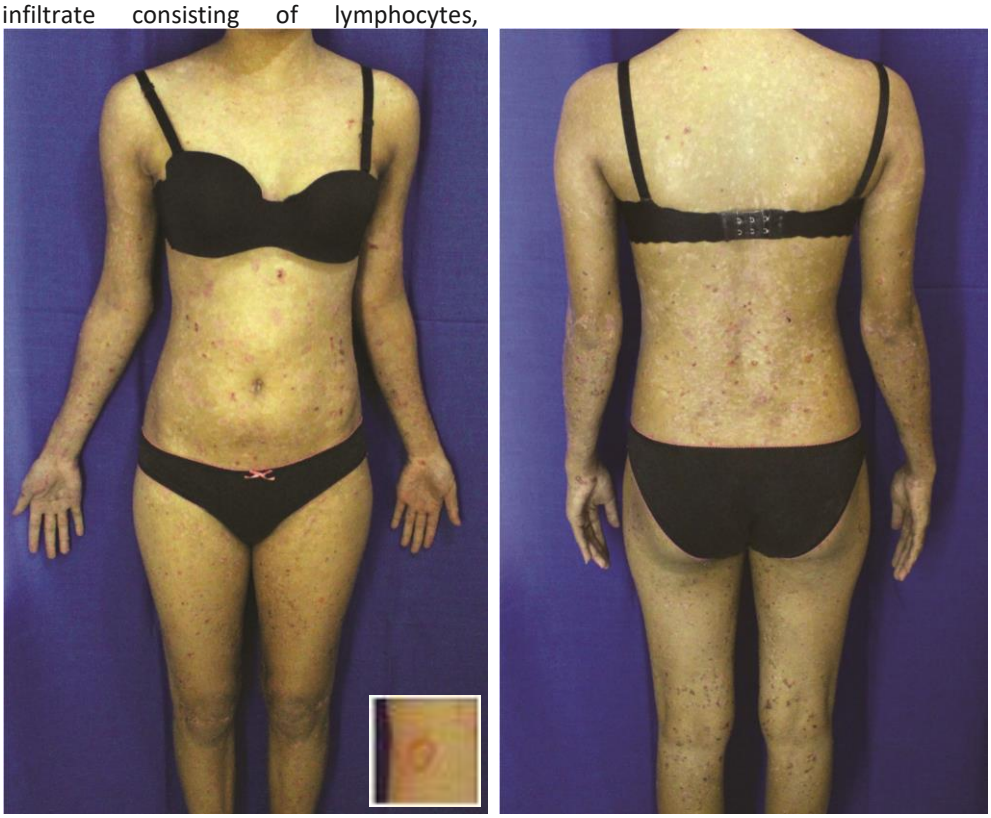

Figure 1. Few tense vesicles and well-defined, irregular erythematous to hypopigmented macules and patches with crusts and erosions on the neck, trunk, upper and lower extremities. Inset: A close up of the tense vesicle

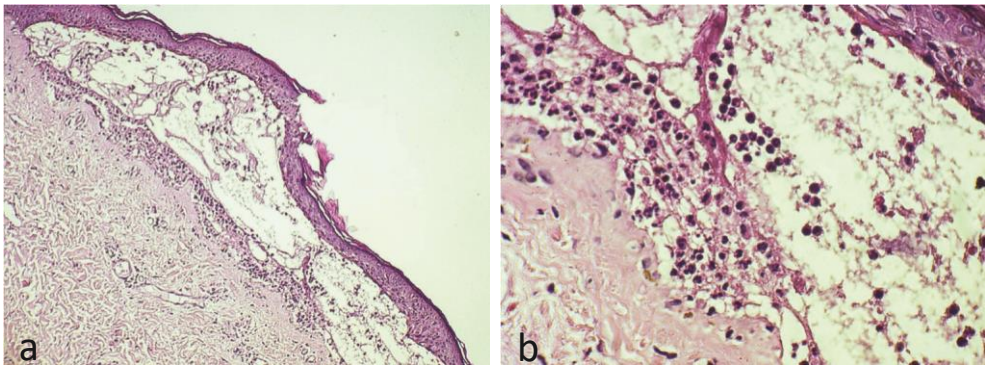

Figure 2. Histopathology of skin punch biopsy specimen (Hematoxylin & Eosin stain) a:10x closer view of the infiltrates within blister; b:40x magnification reveals fibrin, lymphocytes and many neutrophils within the blister)

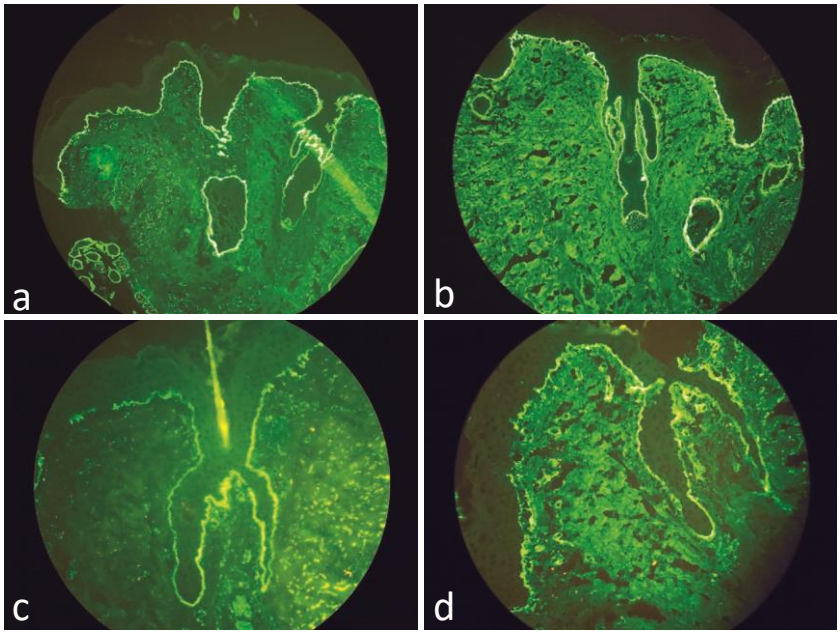

Figure 3. Direct Immunofluouresence showing linear deposits of (a) IgG (+2), (b) C3 (+1), (c) IgM (+2) and (d) fibrinogen (+2).

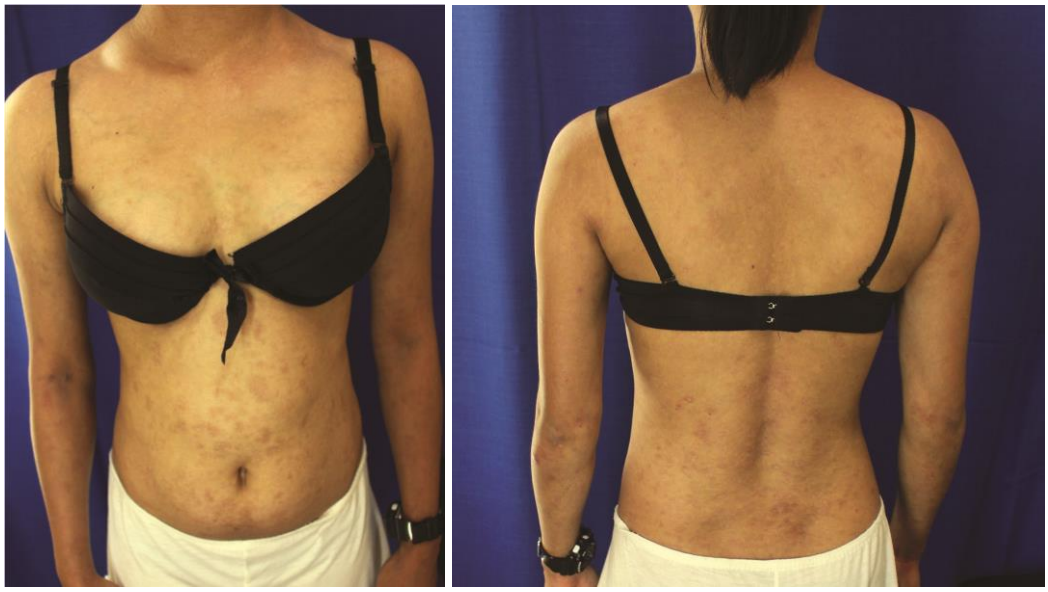

Figure 4. Flattening and hyperpigmentation of lesions after 3 months of treatment with Prednisone and Hydroxychloroquine.

DISCUSSION

Systemic lupus erythematosus is an autoimmune disease in which organs and cells undergo damage initially mediated by tissue-binding autoantibodies and immune complexes.[8] The disease usually affects women in 80-90% of the cases.[6] Seventy-six percent of patients develop cutaneous manifestations during the course of SLE.[3,5] The occurrence of bullous skin lesions in patients with SLE is a well recognized but rare phenomenon and manifests in the second through third decades of life.[7] It occurs in less than 5% of SLE cases.[8] In the Philippines, there were 34 cases from 2011-2016. The pathology of bullous SLE (BSLE) is thought to be associated with antibodies against the non-collagenous domain of collagen VII, as well as other antibodies against different components of the basement membrane.[8-12] Camisa and Sharma (1988) have given the following criteria in diagnosing BSLE: a) a diagnosis of SLE based on fulfillment of the American Rheumatism Association (ARA) criteria for SLE, b) acquired, non-scarring bullous eruption arising on,

but not limited to, sun-exposed areas, c) histologic evidence of a sub-epidermal blister with neutrophilic infiltrates at the basement membrane zone, d) direct immunofluorescence (DIF) of perilesional skin showing IgG, IgA, IgM, and C3 deposits at the basement membrane zone, and (e) evidence of circulating basement membrane zone autoantibodies to type VII collagen.[7,8,13] The diagnosis of bullous systemic lupus erythematosus type 1 requires all of the following. But types 2 and 3 could be diagnosed with the

first four criteria.[14] Our patient fulfilled the first four criteria. Investigations for the presence of autoantibodies to type VII collagen was not done.

BSLE is characterized by a widespread, vesiculobullous eruption that is nonscarring.[7,15,16] Vesicles and bullae are tense and fluid – filled with an erythematous or urticarial background.[17] Clinically, the vesiculobullous lesions are predominantly on the face, neck and upper trunk but may be more widespread, as seen in our patient.[13]

Dapsone is an effective treatment for BSLE, based on a number of studies, and has been shown to have an efficacious response even if given in low doses.[3] It has anti-inflammatory action, mainly by inhibiting the functions of polymorphonuclear leukocytes and of complement activation.[3,5,7,8] Our patient was not started on Dapsone because there was a three-fold increase in the creatinine of our patient as well as there was noted improvement with Prednisone and Hydroxychloroquine. As dapsone often causes renal and hepatic toxicity, corticosteroid alone or with low dose dapsone might be the treatment of choice for BSLE.[3] Corticosteroids are usually required to improve clinical symptoms and laboratory abnormalities, and are still the mainstay for inducing remission in SLE patients.[3] Some studies have shown patients who respond effectively to systemic corticosteroids, although they require relatively high doses. Corticosteroids are used to improve clinical and laboratory abnormalities and a mainstay in inducing remission in patients with SLE. Several studies have shown that a short course of moderate-dose corticosteroids can not only treat active disease but can also help prevent flares in clinically stable but serologically active patients.[19] Corticosteroid treatment, however, is not without its complications.[18] Patients are at risk of a myriad of different problems like fluid retention, hypertension, blurred vision, and infection.[18] It can contribute to atherosclerosis, through adverse effects on metabolic factors such as body fat distribution, blood pressure and glucose metabolism.[18] Other medications that have been studied as treatment options are methotrexate, hydroxychloroquine, cyclophosphamide and mycophenolate mofetil. Azathioprine and biologic agents such as rituximab however, mostly showed that they are useful in controlling the cutaneous lesions and disease activity of SLE.[3] Hydroxychloroquine is the most useful antimalarial drug in the treatment of mucocutaneous, musculoskeletal and constitutional symptoms (such as fatigue and fever) in SLE.[18] It has a good safety profile and toxicity is infrequent, mild and largely reversible.[18]

The prognosis of BSLE is good with variable duration and may be characterized by spontaneous exacerbations and remissions.[7] The prognosis is influenced more by the systemic disease rather than by the eruption hence there is a need to follow closely the systemic disease activity.[7]

CONCLUSION

Patients with BSLE manifest with a widespread symmetrical distribution of vesicular skin lesions frequently favoring the upper part of the trunk, flexural and extensor aspects of the upper extremities, neck and face but may occur anywhere on the cutaneous surface. Treatment with the combination of corticosteroids and hydroxychloroquine was effective in controlling the lesions and manifestations of SLE in our case. BSLE has a good prognosis which is influenced more by systemic disease activity and must be followed closely.[7]

REFERENCES

1. Shirahama S, Yagi H, Furukawa F, Takigawa M. A Case of Bullous Systemic Lupus Erythematosus. *Dermatology.* 1994; 189(suppl I):95-96.
2. Yung A, Oakley A. Bullous systemic lupus erythematosus. *Aust J Dermatol*. 2000, vol 41, no 4, pp. 234-237.
3. Duan L, Chen L, Zhong S, Wang Y, Huang Y, He Y, Chen J, et al. Treatment of Bullous Systemic Lupus Erythematosus. *Journal of Immunology Research*, 2014 Aug. Volume 2015.
4. Rothfield N, Sonthelmer RD. Lupus erythematosus; systemic and cutaneous manifestations. *Clinics in Dermatology*, 2006, vol 24, no 5, pp 348-362.
5. Grover C, Khurana A, Sharma S, Singal A. Bullous Systemic Lupus Erythematosus. *Indian J Dermatol*. 2013 Nov-Dec; 58(6):492.
6. Madiyal A, Ajila V, Hegde S, Babu S, Alva P. Bullous Systemic Lupus Erythematosus: Report of a rare case with oral manifestations and literature review. *Balkan Military Medical Review* 2015; 18(4):134-139.
7. Wojnarowska F, Briggaman RA. Management of Blistering Diseases. Springer Science + Business Media, B.V. 1990; 18:264-275.
8. Dos-Santos CE, Velho PHI, Marques FMM, Werner B, Aragao SC, Filho AR. Bullous systemic lupus erythematosus in a pregnant woman: a case report. *Rev Bras Reumatol.* 2013; 53(5):438-440.
9. Tincopa M, Puttgen KB, Sule S, et al. Bullous Lupus: An Unusual Initial Presentation of Systemic Lupus Erythematosus in an Adolescent Girl. *Pediatric Dermatology*. 2010; 4:373-6.
10. Stith RH, Erickson QL, et al. Bullous Eruption: A Manifestation of Lupus Erythematosus. *Cutis*. 2003; 72:31-7.
11. Fujimoto W, Hamada T, Yamada J, Matsuura H, Iwatsuki K. Bullous Systemic Lupus Erythematosus as an Initial Manifestation of SLE. *J Dermatol*. 2005; 32:1021-27.
12. Ludgate MW, Greig DE. Bullous systemic lupus erythematosus responding to dapsone. *Australas J Dermatol*. 2008; 49:91-3.
13. Aswani V., Vaz B., et al. Bullous Systemic Lupus Erythematosus. *Indian J Dermatol, Venerol and Leprol.* 1993; 59(2):97-100.
14. Yogarajah, M, Sivasambu, B, Jaffe EA. Case reports in Rheumatology Volume 2015. Article ID 930683.
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